Docket No.: PF-0512-1 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1642

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By: _____ Printed: Katherine Stofer

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Lal et al.

Title:	SERINE DEHYDRATASE HOMOLOG		
Serial No.:	09/925,140	Filing Date:	August 08, 2001
Examiner:	Helms, L.	Group Art Unit:	1642

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BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed August 21, 2003, and received by the USPTO on August 25, 2003, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the **$330.00** fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 3-7, 9 and 11 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to **Incyte Pharmaceuticals, Inc., (now Incyte Corporation, formerly known as Incyte Genomics, Inc.)** (Reel 9667, Frame 0465) which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 3-7, 9 and 11
Claims allowed:	(none)
Claims canceled:	Claims 12, 19-26 and 29-46
Claims withdrawn:	Claims 1, 2, 8, 10, 13-18, 27, and 28
Claims on Appeal:	Claims 3-7, 9 and 11 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Rejection under 37 C.F.R. § 1.116, mailed August 21, 2003 and received at the Patent Office on August 25, 2003, has not been entered.

A subsequent Amendment after Final Rejection is filed concurrently herewith. This subsequent Amendment removes issues for appeal. Therefore, it is believed that this subsequent Amendment will be entered.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a human polynucleotide, SEQ ID NO:2, encoding a polypeptide, SDHH, comprising the amino acid sequence of SEQ ID NO:1. SDHH is 329 amino acids in length and has chemical and structural homology with rat liver serine dehydratase (GI 57225); and human liver serine dehydratase (GI 338030) (specification, page 15, lines 15-16). In particular, SDHH and rat liver serine dehydratase share 53.2% identity, and SDHH and human liver serine dehydratase share 56.7% identity (specification, page 15, lines 17-18). SDHH has the serine/threonine dehydratase pyridoxal-phosphate attachment site at E39 (specification, page 15, lines 14-15).

Northern analysis shows the expression of this sequence in various libraries, 48% of which are cancerous, 29% are involved in immune response, and 23% are fetal, cell line, or proliferating (specification, page 15, lines 20-22).

The invention also encompasses naturally-occurring polynucleotide sequences having at least 90% sequence identity to the sequence of SEQ ID NO:2, polynucleotide sequences completely complementary to SEQ ID NO:2 and 90% variants thereof, and ribonucleotide equivalents of these sequences. The invention further encompasses polynucleotides encoding: SEQ ID NO:1; naturally-occurring amino acid sequences having at least 90% sequence identity to the sequence of SEQ ID NO:1; biologically-active fragments of the amino acid sequence of SEQ ID NO:1, wherein said fragments have serine dehydratase activity; and immunologically active fragments of SEQ ID NO:2. The invention further encompasses vectors and cell lines containing polynucleotides encoding SEQ ID NO:1 and variants and fragments thereof, and a method of producing SEQ ID NO:1 and variants and fragments thereof.

(6) ISSUES

1. Whether one of ordinary skill in the art would know how to use the claimed polynucleotide variants, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

2. Whether or not claims 3-7, 9 and 11, as directed to polynucleotide variants and polynucleotides encoding biologically active protein fragments, satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

(8) APPELLANTS' ARGUMENTS

ISSUE 1: Enablement rejections under 35 U.S.C. § 112, first paragraph

Claims 3-7 and 9 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. This rejection of these claims is improper as the specification does adequately describe the invention so that it may be made and/or used by one of skill in the art.

A. Polynucleotides encoding biologically active fragments of SEQ ID NO:1

DROP THIS PART

The Examiner has asserted that "claims 3 and 9 were amended to recite that the biologically active fragment has 'serine hydratase' activity" and that "SEQ ID NO:1 is taught to have 'serine dehydratase' activity not 'serine hydratase' activity" (Final Office Action, page 3). Appellants submit that this was merely a typographical error contained in the amendment filed 3/18/03, an error that the present amendments correct. Claims 3 and 9, as amended herein, recite "a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine dehydratase activity." The response filed on 3/18/03 (pages 6-7) further cites support in the specification for serine dehydratase activity *not* serine hydratase activity. This supports Appellants' present assertion that the previous amendment filed 3/18/03 to claims 3 and 9 to recite "serine hydratase" activity was a typographical error. Thus this aspect of the rejection as it pertains to the claimed polynucleotides encoding biologically active variants is moot.

Appellants note that the specification teaches specific regions of the SDHH polypeptide that are involved in the biological activity. For example, please see the specification at p. 1, lines 15-17, wherein the specification discloses that "[a] motif which interacts with SDH's pyridoxal 5'-phosphate cofactor in several B6 enzymes is considered characteristic of SDH. (Noda et al. 1988, FEBS Lett. 234:331-335."(See Reference No: 1, enclosed). SDHH contains the serine/threonine dehydratase pyridoxal-phosphate attachment site beginning at residue E39 (specification, p. 15, lines 14-15). In addition, serine and threonine dehydratases have another highly conserved domain of 14 residues beginning at I163 of human SDH, which is thought to be the active site for the dehydration reaction in conjunction with the pyridoxal-phosphate attachment site (Noda, page 334, col. 2, and Figure 3). This

region is also well conserved in SDHH. Furthermore, the specification provides an assay for measuring serine dehydratase activity of SDHH (page 50, lines 4-19). Thus one of skill in the art would have ample guidance to the selection of biologically active fragments of SEQ ID NO:1. The skilled artisan would also understand how to use these fragments, for example in the drug screening methods disclosed in the specification at page 39, lines 10-27), without any undue experimentation.

B. Polynucleotide Variants

With respect to the claimed variants, the Examiner has asserted that "while one can screen for enzymatic activity the claims encompass variants that are 90% identical that do not function ... and as such one would not know how to use such polynucleotides" (Final Office Action, page 3). Appellants respectfully point out that the claims are to polynucleotides, not the polypeptides that they encode, and therefore it is the use of the polynucleotides that is relevant. That some of the claims describe the claimed polynucleotides in terms of SEQ ID NO:1 (polynucleotides encoding polypeptides that have 90% identity to SEQ ID NO:1) as noted by the Examiner (Final Office Action, page 3), does not change the fact that the claims are directed to polynucleotides, not polypeptides. The specification recites many instances where a polynucleotide may be used, in which one of skill in the art would recognize that useful SDHH-encoding polynucleotides would encompass those encoding SDHH or its naturally-occurring variants, whether or not those encoded polypeptides had enzymatic activity.

For example, "the nucleotide sequences encoding SDHH may be useful in assays that detect the presence of associated disorders" (specification, page 36, lines 18-19). The specification (page 25, lines 16-18) discloses that "SDHH is expressed in tissues which are cancerous, proliferating, or involved in immune response. Therefore, SDHH appears to play a role in disorders of metabolism and cancer." Thus, these polynucleotide sequences may be utilized in assays to detect the presence of metabolism disorders or cancer. The specification further (page 35, lines 9-11) discloses that "[t]he polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of SDHH may be correlated with disease." Indeed one of skill in the art would recognize that whether or not the polynucleotide encoded an SDHH protein having enzymatic activity, the use of the polynucleotide would be the same.

In another example, the polynucleotides are used as research tools. The specification (page 35, lines 22-23) discloses that "probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the SDHH encoding sequences." Upon reading this specification, one of skill in the art would recognize that "at least 50% sequence identity" would encompass the 90% variants recited by the claims. The skilled artisan would also understand that the claimed variants would be useful as probes regardless of the enzymatic activity or lack thereof of the encoded protein. The specification further discloses that "[t]he polynucleotide sequences encoding SDHH may be used in Southern or Northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and ELISA assays; and in microarrays utilizing fluids or tissues from patients" (specification, page 36, lines 13-16). Methods of using polynucleotides such as those encoding SDHH are well known in the art, and guidance for these methods is also provided throughout the specification (e.g., page 37, lines 18-31; page 47, lines 16-33; and page 48, lines 1-20). Thus one of ordinary skill in the art would know how to use the claimed polynucleotide variants encoding SDHH polypeptides with or without enzymatic activity.

The specification further discloses the use of polynucleotide sequences in microarray technology (specification, page 37, line 32 to page 38, line 6). This technology can be used to "identify genetic variants, mutations, and polymorphisms" (specification, page 38, line 3). One of skill in the art would recognize that the information gained in these types of experiments could be useful in determining gene function, understanding the genetic basis of a disorder, or to diagnose a disorder. The experimental processes employed would be the same regardless of whether the polypeptide encoded by the polynucleotide sequence used in the microarray possessed enzymatic activity.

In addition, another well-known use for microarrays containing the claimed polynucleotide variants is in expression profiling. In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the naturally occurring polynucleotides at issue, are tools essential to any technology that uses expression profiling.

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (July 1999) (Reference No. 2, enclosed):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656.)

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999) (Reference No: 3, enclosed); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000) (Reference No: 4, enclosed).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes,5.John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being

used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999) (Reference No. 5, enclosed). One of skill in the art would recognize that the most powerful arrays would therefore include naturally occuring polynucleotide variants (e.g. single nucleotide polymorphisms, allelic variants, etc.) whether or not those variant polynucleotides encoded a functional protein.

As stated above, the specification discloses many uses of the claimed polynucleotides, including the SEQ ID NO:2 polynucleotide variants. Further, the specification specifically describes the use of the claimed polynucleotides in microarray technology. This technology was well known in the art at the time that the instant application was filed, as evidenced by the disclosure in the specification, for example at page 35, lines 21-26. Thus, one of skill in the art, upon reading this specification, would know how to use the claimed SDHH-encoding polynucleotides. Furthermore, one of skill in the art would recognize that the use of a *naturally occurring variant* SDHH-encoding polynucleotide would be the same, whether or not the encoded variant SDHH protein had enzymatic activity.

For at least the reasons set forth above, the specification provides enablement of the claimed subject matter, and reversal of this rejection is therefore requested.

ISSUE 2: Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 3, 6-7, 9, and 11 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention, at the time the application was filed.

With respect to the claimed polynucleotides encoding biologically active fragments of SEQ ID NO:1, the Examiner has stated that "the claims recite serine hydratase activity not serine dehydratase activity and as such one skilled in the art would not know how to test the polypeptides for activity" (Final Office Action, page 4). As stated in the previous section, the amendment of 3/18/03 which amended claims 3 and 9 to recite a biological activity of serine hydratase rather than serine dehydratase was a typographical error. The present amendments to claims 3 and 9 correct that typographical error.

Thus this aspect of the rejection as it pertains to the claimed polynucleotides encoding biologically active fragments of SEQ ID NO:1 is moot.

Appellants further note that the specification teaches specific regions of the SDHH polypeptide that are involved in the biological activity. For example, please see the specification at p. 1, lines 15-17, wherein the specification discloses that "[a] motif which interacts with SDH's pyridoxal 5'-phosphate cofactor in several B6 enzymes is considered characteristic of SDH. (Noda et al. 1988, FEBS Lett. 234:331-335)." SDHH contains the serine/threonine dehydratase pyridoxal-phosphate attachment site beginning at residue E39 (specification, page 15, lines 14-15). In addition, serine and threonine dehydratases have another highly conserved domain of 14 residues beginning at I163 of human SDH, which is thought to be the active site for the dehydration reaction in conjunction with the pyridoxal-phosphate attachment site (Noda, page 334, col. 2, and Figure 3). This region is also well conserved in SDHH. Furthermore, the specification provides an assay for measuring serine dehydratase activity of SDHH (page 50, lines 4-19). One of skill in the art would have ample guidance to the selection of biologically active fragments of SEQ ID NO:1.

Given that one of ordinary skill in the art has been provided with ample guidance towards selecting polynucleotides encoding biologically active fragments of SEQ ID NO:1, it is not necessary to list all possible such fragments, and such a list would needlessly clutter the specification.

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With respect to the claimed polynucleotide variants, the Examiner has asserted that "the skilled artisan cannot envision the detailed structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred" (Final Office Action, page 5).

To address this issue, one must first set forth the proper legal standard. The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published December 21, 1999 (Interim Guidelines), which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one skilled in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met.

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The Specification provides an adequate written description of the claimed polynucleotide variants

SEQ ID NO:2 is specifically disclosed in the application (specification, page 15, lines 29-31). The Specification further describes variant sequences of SEQ ID NO:2 that have at least about 90% identity to SEQ ID NO:2 (specification, e.g., page 15, line 33 through page16, line 7). In addition, SEQ ID NO:1 (the amino acid sequence of SDHH) is specifically disclosed in the application (specification, page 15, lines 11-24). The specification further describes variants at least 90% identical to SEQ ID NO:1. Given SEQ ID NO:1 and SEQ ID NO:2, one skilled in the art would recognize naturally-occurring variants of SEQ ID NO:1 or SEQ ID NO:2 having 90% sequence identity to SEQ ID NO:1 or SEQ ID NO:2.

With respect to the written description of the claimed polynucleotide variants, the Examiner has asserted that "the general knowledge in the art does not provide any indication of how the structure of one variant is representative of unknown variants" (Final Office Action, page 4). Appellants respectfully emphasize that the claimed variant polynucleotides are "naturally occurring" and as such, the scope of the claimed variants in narrowed to a finite set, rather than all possible variants that could be produced

using recombinant DNA techniques. The specification describes several types of naturally occurring variants (e.g., allelic variants and altered nucleic acid sequences). An "allelic variant is described as "an alternative form of the gene encoding SDHH. Allelic variants ... may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered" (specification, p. 6, lines 13-16). "Altered" nucleic acid sequences are described as "sequences with deletions, insertions, or substitutions of different nucleotides" (specification, p. 6, line 21 to p. 7, line 4). These descriptions underscore that the claimed polynucleotide variants are limited to "*naturally occurring*" polynucleotide variants and provide guidance as to what types of variants are encompassed in the claims.

The scope of the of the claimed variants is further limited by the recitation in the claims of a polynucleotide "at least 90% identical to the polynucleotide sequence of SEQ ID NO:2" or encoding a polypeptide "at least 90% identical to the amino acid of SEQ ID NO:1." The specification discloses the sequences of SEQ ID NO:1 and SEQ ID NO:2 (specification, pages 54-55). The specification also provides guidance in determining percent identity (specification, page 10, lines 11-27). These and other methods are also well known in the art. One of skill in the art would therefore readily recognize a polynucleotide variant having 90% identity to SEQ ID NO:2 or to a polynucleotide encoding SEQ ID NO:1.

Appellants submit that with the disclosure of the sequences of SEQ ID NO:1 and SEQ ID NO:2, the recitation of "naturally occurring" and "at least 90% identical" in the claims, and the routine use of sequence comparison analysis methods by persons of skill in the art, the claimed polynucleotide variants are adequately described. As stated in Section 2163.02 of the Manual of Patent Examining Procedure "one must define a compound by 'whatever characteristics sufficiently distinguish it.'" Persons of skill in the art routinely use percent identity of one sequence to another to describe a sequence. Appellants submit that the percent identity limitation coupled with the limitation that the variant be "naturally occurring" would serve to adequately describe to one of skill in the art the claimed variants so as to sufficiently distinguish them from other unrelated sequences.

Given the information provided by SEQ ID NO:1 (the amino acid sequence of SDHH) and SEQ ID NO:2 (the polynucleotide sequence encoding SDHH), one of skill in the art would be able to routinely obtain polynucleotides encoding "a naturally occurring amino acid sequence having at least

90% sequence identity to the sequence of SEQ ID NO:1" or a polynucleotide with 90% identity to SEQ ID NO:2. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application, for example, at page 13, lines 3-26; page 35, lines 14-26; and Example VI at page 47.

Thus, one of skill in the art need not make and test vast numbers of polynucleotides that are based on the polynucleotide sequence of SEQ ID NO:2. Instead, one of skill in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides that already exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain the claimed variant polynucleotides of SEQ ID NO:2 or polynucleotides which encode variants of SEQ ID NO:1. One of skill in the art would also understand how to recognize the claimed variants within a sequence database, for example, by using the techniques described in the specification at page 42, lines 5-25.

Given the sequences of SEQ ID NO:1 and SEQ ID NO:2, one of ordinary skill in the art could readily identify a naturally-occurring polynucleotide sequence having at least 90% sequence identity to the sequence of SEQ ID NO:2, or a polynucleotide encoding a naturally occurring polypeptide having at least 90% identity to SEQ ID NO:1 using well known methods of sequence analysis, without any undue experimentation.

Accordingly, the Specification provides an adequate written description of the recited polynucleotides.

B. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written

description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA

of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 3 or independent claim 11 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of...a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid of SEQ ID NO:1...
>
> 11. An isolated polynucleotide selected from the group consisting of...a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of the polynucleotide sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polypeptides encoded by the polynucleotides recited by the claims. The polynucleotides in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

C. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Board's attention is directed to the previously submitted reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally

identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding serine dehydratases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as serine dehydratases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, a polynucleotide encoding a polypeptide comprising "a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 329 amino acid residues). This variation is far less than that of all potential serine hydratases related to SEQ ID NO:1, i.e., those serine dehydratases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structures of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and reversal of this rejection is therefore requested.

(9) CONCLUSION

Appellants request that the rejections of the claims on appeal be reversed for at least the reasons above.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

This brief is enclosed in triplicate

Respectfully submitted,
INCYTE CORPORATION

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Enclosures:

1. Noda et al. 1988, FEBS Lett. 234:331-335
2. Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, Xenobiotica 29:655-691 (July 1999)
3. Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).
4. Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999);
5. John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999).
6. Brenner et al., Proc. Natl. Acad. Sci. 95:6073-78 (1998)

APPENDIX - CLAIMS ON APPEAL

3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine dehydratase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1.

4. An isolated polynucleotide of claim 3 encoding the amino acid sequence of SEQ ID NO:1.

5. An isolated polynucleotide of claim 4 having the polynucleotide sequence of SEQ ID NO:2.

6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

9. A method of producing a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said biologically active fragment has serine dehydratase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein said immunogenic fragment generates an antibody that specifically binds to SEQ ID NO:1, the method comprising:

i) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding said polypeptide, and

ii) recovering the polypeptide so expressed.

11. An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,

c) a polynucleotide completely complementary to a polynucleotide of a),

d) a polynucleotide completely complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).